Relative Inhibitory Effect of Various Compounds on the Rate of Polymerization of Vinyl Acetate. III. Effect of Compounds of Various Classes.

INTRODUCTION

A study of the relative free-radical inhibitory effect of many anticancer compounds of various classes has been made and will be reported elsewhere. Vinyl acetate containing various concentrations of anticancer compounds was polymerized in the presence of benzoyl peroxide as in previous investigations.[1-3] However, in order to explain the free-radical inhibitory activity of these compounds, it is necessary to compare their chemical structures with those of simpler compounds which have already been studied. Therefore, a brief summary of previous and present work on eight of the more important classes of conventional inhibitors is presented in this note.

EXPERIMENTAL

A 10-ml portion of vinyl acetate (Gulf Oil Canada, commercial grade) containing 0.0200 g of recrystallized benzoyl peroxide[4] and a known amount of inhibitor were polymerized in a 150 mm × 25 mm test tube immersed in a stirred water bath at 70.0 ± 0.05°C (method B[2]). The inhibition factor, expressed in minutes (delay in the spontaneous polymerization) per ppm of inhibitor was calculated as previously.[2,3] In order to obtain more reproducible results, specks of dirt in the sample, imperfectly cleaned test tubes, imperfections in the glass surface, and impurities in the initiator must be reduced to a minimum. Immediately after each test, the test tube should be cleaned with ethyl acetate, then with hot alcoholic KOH for several hours, and finally with hot chromic acid, distilled water, and redistilled methanol. The test tubes should be dried with a hair drier and stored in a hot oven until a few minutes before being used.

RESULTS

A summary of previous and current results on eight important classes of free-radical inhibitors is given in Table I. Typical examples of the strongest known inhibitors in each class are included. The inhibition factors for certain compounds have not yet been determined in a vinyl acetate polymerization system and consequently they had to be calculated from work done with methyl methacrylate or acrylonitrile. These values are probably reasonable approximations but they are not equivalent, in accuracy, to experimentally derived data.

From the data given in Table I, it will be noted that unsaturated hydrocarbons range from extremely strong inhibitors (e.g., *trans*-1,3,5,-hexatriene) to extremely weak (e.g., hexene-1). It was previously established that the value of the inhibition factor is determined primarily by the number and relationship of the double and triple bonds.[2,3] The effect of the double bond is usually of the same order of magnitude as that of the triple in both conjugated and isolated systems. For example, the inhibition factors of typical mono-olefins (*cis*- and *trans*-hexene-2) average 22% higher than that of the corresponding acetylene (hexyne-2), while the factors of some typical conjugated diolefins (2,5-dimethyl-2,4-hexadiene and chloroprene) average within 10% of those of diacetylene and the vinylacetylenic compound, 2-methyl-1-buten-3-yne. Small, saturated substituent groups, on the other hand, usually have little effect. However, as the saturated groups become larger, steric effects become more important. The inhibition factor (calculated on a weight basis) increases rapidly with increase in the number of double and triple bonds up to a certain limit, especially in conjugated systems. The maximum value was obtained when there were three conjugated double bonds, i.e., *trans*-1,3,5-hexatriene. Four conjugated groups, e.g., 1,3,7-octatrien-5-yne, did not exhibit stronger inhibition

TABLE I
Inhibition Factors of Compounds of Various Classes
Using a Vinyl Acetate Polymerization System at 70°C

Compounds	Inhibition factor, min/ppm	Activity of original V.A., sec	Concn range, ppm
Unsaturated Hydrocarbons			
Hexene-1[3]	0.00203	982	0–6000
cis-Hexene-2[3]	0.0053	970	0–3600
Hexyne-2[3]	0.0051	919	0–3600
1,5-Hexadiene[3]	0.0092	990	0–1800
1,5-Hexadiyne[3]	0.0385	969	0–400
1,8-Nonadiyne[3]	0.0094	924	0–2800
4-Chloro-1,2-butadiene[3]	0.0286	977	0–700
2-Chloro-1,3-butadiene[3]	0.521	974	0–42
2,5-Dimethyl-2,4-hexadiene[3]	0.765	970	0–20
Diacetylene[3]	0.69		
2-Methyl-1-buten-3-yne[3]	0.69	919	0–36
trans-1,3,5-Hexatriene[2]	1.57	770	0–12
Divinylacetylene[2]	1.33	790	0–15
1,3,7-Octatrien-5-yne[1]	1.34[a]		
Phenolic Compounds			
Hydroquinone[3]	1.01	842	0–40
p-tert-Butylcatechol	0.92	895	0–20
1,2,4-Trihydroxybenzene[5]	1.1[b]		
1,5-Naphthalenediol[5]	0.7[b]		
Quinones			
p-Benzoquinone[6]	0.83[b]		
Amines			
Diphenylamine	0.77	880	0–7
1-Naphthylamine[6,7]	0.7[b]		
Stable Free Radicals			
2,2-Diphenyl-1-picrylhydrazyl[6]	1.17		
Sulfur Compounds			
Divinyl sulfide[2]	0.05[c]		
Thiophene[2]	0.003[c]		
Benzene thiol[6]	0.1[b]		
Carbonyl Compounds			
Acetaldehyde[2]	0.013[c]		
Acetone[2]	0.0011	770	0–5000
Crotonaldehdye[2]	0.062	775	0–200
Metallic Salts			
Cupric acetate monohydrate	5–14	870–900	0–0.7
Copper resinate (8.5% Cu)	2.4	840	0–3

[a] Calculated from data on acrylonitrile.
[b] Calculated from data on methyl methacrylate.
[c] Calculated from data on activity test A for vinyl acetate.[2]

(on a weight basis) than three groups, e.g., 1,3-hexadien-5-yne, in the polymerization of acrylonitrile.[1] Consequently, it appears that a further increase in the number of conjugated groups is unlikely to produce a substantial increase in the inhibition factor.

When the double or triple bonds are isolated or cumulative, the inhibition factor decreases by one to two orders of magnitude when compared to conjugated systems. For

example, the inhibition factor of 1,5-hexadiene (isolated double bonds) is only 1.2% of that of 2,5-dimethyl-2,4-hexadiene, and the factor for 4-chloro-1,2-butadiene (cumulative double bonds) is only 5.5% of that of 2-chloro-1,3-butadiene. The presence of a second ethylenic or acetylenic group in a compound with isolated unsaturation causes a synergistic effect on the first group and this effect decreases as the two unsaturated groups become farther separated in the molecule.

From an industrial standpoint, the polyhydric phenols are probably the most important free-radical inhibitors. There is little difference between the inhibition factors of the corresponding dihydric and trihydric phenols but polyhydric phenols are much stronger than the monohydroxybenzenes such as phenol and *p*-methoxyphenol.[3,5,6] There are also, in general, relatively small differences between the strongest dihydroxybenzenes and the strongest dihydroxynaphthalenes[5] but there are very great differences between the various isomers. In the case of both the di- and trihydroxybenzenes, the *para*-isomers are the strongest, the *ortho*- are somewhat weaker, and the *meta*-isomers are very much weaker.[5] Hydroquinone, which is probably the most widely used inhibitor, has an inhibition factor of 1.01 min/ppm. The *ortho*-addition of another hydroxyl group to hydroquinone, i.e., 1,2,4-trihydroxybenzene, increases the inhibition factor only slightly.[5] Among the naphthols, 1-naphthol is very much stronger than 2-naphthol and the 1,5- and 1,6-analogs are approximately the same strength. 1,4-Naphthalenediol, on the other hand, is extremely weak.[5]

p-Benzoquinone is slightly weaker than hydroquinone but it is much stronger than 1,4-naphthoquinone, which in turn is much stronger than 1,4-anthraquinone.[5,6] The addition of two chlorine atoms to *p*-benzoquinone at the 2,6-positions enhances the inhibition factor by about 20%.[6]

Aromatic amines, such as diphenylamine, are widely used for inhibiting monomers such as vinyl acetate against polymerization during long storage or distillation. In general many aromatic amines are relatively strong inhibitors while the aliphatic analogs are weak.[6,7] The difference between the strongest phenylamines and the strongest naphthylamines is not great. The cyclic amine, phenothiazine, is much weaker than the strongest aromatic amines. Diphenylamine (with an inhibition factor of 0.77 min/ppm) is somewhat weaker than hydroquinone, but *o*-phenylenediamine, which is the strongest amine inhibitor for methyl methacrylate found by Yates and Ihrig,[7] appears to be somewhat stronger than hydroquinone. Aliphatic amines (e.g., N-nitrosodimethylamine) and amides (e.g., hexamethylphosphamide) are generally almost without inhibitory effect on the polymerization of methyl methacrylate.[6]

Stable free radicals are still relatively rare but one of the more common ones, 2,2-diphenyl-1-picrylhydrazyl, was studied.[6] It was found to be a little stronger than hydroquinone and, therefore, must be classed as a very strong inhibitor. Some stable free radicals are of biologic importance and a few have been reported to exhibit antitumor activity in mice.[8,9]

Sulfur compounds are widely used industrially as chain transfer agents and antioxidants. None of the sulfur compounds investigated[2,6] was found to be a strong inhibitor. Aromatic thiols are considerably stronger than the aliphatic analogs. For example, the inhibition factor of benzene thiol appears to be two to four times as great as that of 1-butane thiol or *n*-dodecyl mercaptan in the polymerization of methyl methacrylate,[6,10] and it is about one-tenth that of hydroquinone.[6] Cyclic sulfur compounds such as thiophene are extremely weak[2] but phenothiazine, which contains both sulfur and nitrogen in the ring, is considerably stronger.[6] Aliphatic sulfides are also weak. Even with the contribution of two vinyl groups, divinyl sulfide[2] has an inhibition factor of only 0.05/ppm.

Carbonyl compounds are extremely weak inhibitors and are usually classed as chain transfer agents. Saturated aldehydes, e.g., acetaldehyde, are one order of magnitude stronger than saturated ketones, e.g., acetone. However, when there is an ethylenic group conjugated with the carbonyl of an aldehyde, e.g., crotonaldehyde, the inhibition factor increases by about one order of magnitude.[2]

Another important class of chain transfer agents are the halogenated hydrocarbons, e.g., 1,1-dichloroethane and 1,1,2-trichloroethane.[11] These compounds reduce the average molecular weight without greatly retarding the polymerization.

Mixtures of two inhibitors have also been studied.[6] It was found that when the two components were of a different chemical class, some synergistic inhibition was obtained. However, as the constitutions of the components became more similar, the synergism decreased. It is interesting to note that synergistic inhibition of cell growth also has been observed many times when certain mixtures of dissimilar anticancer compounds have been used.

Some metallic salts are also strong inhibitors. For example, cupric acetate was found to have an inhibition factor varying from 5 to 14 min ppm. This value is very much higher than that for any organic compound so far studied. Different inhibition values were obtained with different samples of vinyl acetate, indicating that a part of the copper ion was reacting with a species that was varying, e.g., impurities in the vinyl acetate. In some oxidation systems, copper ions are believed to act by a chelation mechanism. The latter is, of course, entirely different from the mechanism by which many organic inhibitors are known to work, e.g., by hydrogen abstraction from the inhibitor. Antimony pentachloride is also a relatively strong inhibitor being nearly half as strong as hydroquinone.[6] However, antimony trichloride is very weak, indicating that the valence state of the metal is very important.

The inhibitory effect of a few compounds was studied using methyl methacrylate[6] and vinyl chloride[12] as well as vinyl acetate as monomers. For many of these inhibitors, the ratios (but not the absolute values) of the inhibition factors were quantitatively or semiquantitatively the same for methyl methacrylate or vinyl chloride as for vinyl acetate. With some inhibitors for methyl methacrylate, the relationship was only qualitative. However, in every instance, a compound that was found to be a strong inhibitor for one vinyl monomer was also found to be a strong inhibitor for the other vinyl monomers. Thus, the chemical structure of the vinyl monomer, and consequently the free radicals derived from it, also affect to some extent the value of the inhibition factor. Caution must, therefore, be exercised in extrapolating our inhibition factors to biologic systems in which the chemical compositions of the free radicals are largely unknown.

REFERENCES

1. K. K. Georgieff, *J. Polym. Sci.*, **14**, 589 (1954).
2. K. K. Georgieff and G. S. Shaw, *J. Appl. Polym. Sci.*, **5**, 212 (1961).
3. K. K. Georgieff, K. G. Blaikie, and R. C. White, *J. Appl. Polym. Sci.*, **8**, 889 (1964).
4. K. K. Georgieff, *J. Appl. Polym. Sci.*, **8**, 507 (1964).
5. R. C. Caldwell and J. L. Ihrig, *J. Amer. Chem. Soc.*, **84**, 2878 (1962).
6. K. K. Georgieff, *J. Appl. Polym. Sci.*, **9**, 2009 (1965).
7. W. R. Yates and J. L. Ihrig, *J. Amer. Chem. Soc.*, **87**, 710 (1965).
8. N. M. Emanuel, *Proc. 5th Intern. Congr. Biochem., Moscow*, **4**, 58 (1961).
9. N. P. Konovalova, G. N. Bogdanov, V. B. Miller, M. B. Neiman, E. G. Rozantsev, and N. M. Emanuel, *Dokl. Akad. Nauk SSSR*, **157**, 707 (1964).
10. J. L. O'Brien and F. Gornik, *J. Amer. Chem. Soc.*, **77**, 4757 (1955).
11. M. K. Lindemann, in *Vinyl Polymerization*, Vol. 1, Part I, G. E. Ham, Ed., Marcel Dekker Inc., New York, 1967, pp. 238–240.
12. K. K. Georgieff, *J. Appl. Polym. Sci.*, **8**, 2213 (1964).

K. K. GEORGIEFF

Research Laboratories
Gulf Oil Canada Ltd.
Shawinigan Chemicals Division
Ste-Anne-de-Bellevue, Quebec, Canada

Received March 13, 1970